Daily Aspirin Use Reduces Risk of Fibrosis Progression in Patients With Nonalcoholic Fatty Liver Disease, Providing New Uses for an Old Drug

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Key words: NAFLD, Fibrosis, Cirrhosis, Aspiring

Disclosures: Dr. Vilar-Gomez declares no conflicts of interests. Dr. Chalasani declares no relevant conflicts of interests for this invited editorial. For full disclosure, Dr. Chalasani has ongoing paid consulting activities (or had in preceding 12 months) with NuSirt, Abbvie, Afimmune (DS Biopharma), Allergan (Tobira), Madrigal, Coherus, Siemens, Centurion, and Genentech. These consulting activities are generally in the areas of nonalcoholic fatty liver disease and drug hepatotoxicity. Dr. Chalasani receives research grant support from Exact Sciences, Intercept, and Galectin Therapeutics where his institution receives the funding. Over the last decade, Dr. Chalasani has served as a paid consultant to more than 35 pharmaceutical companies and these outside activities have regularly been disclosed to his institutional authorities.

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Nonalcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease, which affects roughly 26% of US population - about 80 million Americans.[1] It is estimated that 20-30% of NAFLD population may develop nonalcoholic steatohepatitis (NASH), which is considered a leading cause of end-stage liver disease, hepatocellular carcinoma and liver transplantation.[2] Since obesity and type 2 diabetes mellitus (T2DM) prevalence are expected to increase in the upcoming years, studies project a significant increase in NAFLD-related morbidity and mortality in the United States.[1, 3] The fibrosis stage is a major determinant not only of long-term liver-related outcomes and mortality, but also has been associated with increased risk of cardiovascular events and cancers. Thus, pharmacological therapies targeting fibrosis pathways are ideal candidates to prevent or reduce fibrosis progression and subsequently disease burden.[4] Despite the rapidly growing burden of NAFLD/NASH, medical strategies to ameliorate fibrosis including lifestyle or pharmacological interventions are effective only in a limited number of patients.[2, 5]

This is the author's manuscript of the article published in final edited form as:
Vilar-Gomez, E., & Chalasani, N. (2019). Daily Aspirin Use Reduces Risk of Fibrosis Progression in Patients With Nonalcoholic Fatty Liver Disease, Providing New Uses for an Old Drug. Clinical Gastroenterology and Hepatology. https://doi.org/10.1016/j.cgh.2019.06.032

It is estimated that tens of millions of adults regularly take aspirin in the US. Low-dose regular aspirin use has shown excellent benefits in reducing the risk of heart/stroke attacks and gastrointestinal cancers in selected high-risk adults who are not at increased risk for bleeding.[6, 7] New experimental and clinical evidence is now emerging that the drug may help to curb liver and cardiac[8] fibrosis as well as reduce risk of hepatocellular carcinoma.[9, 10]

In the present issue of ***Clinical Gastroenterology and Hepatology***, Simon et al[11] examined the relationship between regular use of aspirin and the risk of fibrosis in adults with biopsy proven NAFLD. A primary cross-sectional analysis determined the prevalence of fibrosis on liver histology in 361 NAFLD patients, and two secondary longitudinal analyses further explored the cumulative incidence of advanced fibrosis (F3-4) as determined by serum biomarkers (n=317) or liver histology (n=72) among individuals with early stages of fibrosis (F0-2) at enrollment biopsy. Covariate-adjusted multivariable models were constructed including well-recognized confounders, and aspirin use was modeled as a time-varying covariate to overcome the immortal time bias. A total of 151 patients were identified as regular users of aspirin and were compared to 210 non-regular users. Both cross-sectional and longitudinal analyses showed independent and negative associations between fibrosis severity and daily aspirin use. In the cross-sectional analysis, regular use of aspirin lowered the risk of fibrosis (adj. OR: 0.54, 95% CI: 0.31-0.82) even after controlling by concurrent use of non-aspirin NSAIDs and other confounders. The longitudinal analysis also showed that daily aspirin use was associated with significantly lower incidence of advanced fibrosis (adj. HR: 0.63, 95% CI 0.43-0.85). To authenticate this finding, researchers also examined the risk of disease progression among patients with paired liver biopsies. This subgroup analysis showed that risk of advanced fibrosis remained consistently lower among daily aspirin users (adj. HR: 0.64, 95% CI 0.50-0.80) than non-users. The researchers further tested if the association between pre- and post-enrollment aspirin use and lower risk of fibrosis could be exposure duration-dependent, and found that longer aspirin consumption was associated lower risk of fibrosis progression, and at least 2 years of regular aspirin use was required to detect beneficial effects. These provocative observations are of potential clinical utility.

Chronic inflammation is a known risk factor for liver disease progression or cancer, especially in patients who suffer from chronic inflammatory processes such as chronic viral

hepatitis, NAFLD or inflammatory bowel disease. In recent years, preclinical models of chronic liver disease have suggested that platelets play a central role in liver inflammation and fibrosis.[12] Thus, a dual anti-platelet and anti-inflammatory function of low-dose aspirin (81-325 mg) may provide foundational pathophysiological basis to explain its antifibrotic and chemopreventative benefits. Aspirin modulates cyclooxygenase-2 (COX-2), a key enzyme that induces pro-inflammatory prostaglandins, including prostaglandin E2 which increases cellular proliferation, promotes angiogenesis, and increases resistance to apoptosis.[13] In addition, aspirin also inhibits cyclooxygenase-1 (COX-1) expression which controls prostaglandin levels involved in platelet activation and protection of gastrointestinal mucosa. These effects, along with other non-COX mechanisms affecting the expression of other inflammatory and pro-tumoral molecules, may explain the dramatic effect of aspirin on liver fibrosis progression or cancer rates. **Figure 1** illustrates physiologic mechanisms to explain potential antifibrotic and chemopreventative effects of aspirin.

Consistent with RCTs and other observational studies, long-term use of low-dose aspirin is associated with a dramatic reduction in the incidence of heart attack, stroke and gastrointestinal and liver cancers.[9, 14] However, heart- and cancer-related benefits of aspirin are offset by the risk for serious bleeding events. Even at low or very low doses, aspirin has shown a 59% increased risk of major gastrointestinal bleeding and 33% increased risk of hemorrhagic stroke, particularly in patients at high risk, including those with prior GI bleeding or ulceration, prior complications from aspirin use, or known bleeding diathesis.[15] These findings prompted the US Preventive Services Task Force to recommend aspirin use only in adults aged between 50-69 years with determined cardiovascular risk profile to prevent colorectal cancer.[14]

While current study provides provocative data supporting and extending the currently available literature, there are important clinical and methodologic limitations that deserve further discussion. First, major bleeding rates were not reported among aspirin users vs. non-users. It is particularly important as these events have a notable influence on acceptability and adherence during long-term aspirin use. Second, the optimum antifibrotic dose of aspirin remains in doubt. Third, benefits and harms of prophylactic use of aspirin among patients with high burden disease such as cirrhosis, type 2 diabetes and age $\geq$ 70 years are unknown. Fourth, although authors showed the beneficial effect of daily aspirin use on fibrosis progression was unchanged after

controlling by other medications with recognized disease-modifying effects such as metformin,[16] vitamin E,[17, 18] pioglitazone[18] and statins, drug-drug additive and interaction effects were not explored. Finally, the present study lacked detailed information regarding non-aspirin NSAIDs dosage and duration, and the use of other anti-platelet drugs which highlight the need for further studies exploring the impact of these medications alone or in combination with aspirin for prevention of fibrosis.

The present study provides further clinical support to the emerging evidence for a critical pathological link between platelet activation, pro-inflammatory environment and liver fibrosis and hepatocellular carcinoma. While certainly promising, aspirin use to improve liver fibrosis or liver outcomes in NAFLD is not ready for prime time in clinical practice. Further high-quality cohort studies as well as randomized controlled studies are required to explore the beneficial effects of aspirin or even other anti-platelets or non-aspirin NSAIDs in preventing hepatic fibrosis and its impact on long-term clinical outcomes among NAFLD patients. Even if multiple other studies show benefits for daily aspirin use, considering that patients with NAFLD cirrhosis are at higher risk for bleeding complications, one needs to carefully consider which NAFLD subpopulation derive the most benefit from daily aspirin use.

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FIGURE LEGEND

Figure 1. Mechanisms of action of aspirin.

Aspirin in low doses (81-325 mg/day) irreversibly inhibits platelet TXA2 synthesis, however, high doses (2-3 g/day) are required to inhibit formation of PGI2. High doses irreversibly inactivate both isoforms of the COX enzymes (COX-1 and COX-2). The gastrointestinal adverse effects of aspirin and nonsteroidal anti-inflammatory drugs are mainly a result of COX-1 inhibition. Aspirin has been found to inhibit IκB kinase β and prevent NF-κB activation. Inhibition of both pathways may affect the transcription of several proteins involved in inflammatory responses and angiogenesis which may contribute to the observed antifibrotic and anticancer effects.

Abbreviations: PGG2, prostaglandin G2; COX, cyclooxygenase; PGH2, prostaglandin H2; TXA2, thromboxane A2; PGE2, prostaglandin E2; PGI2, prostaglandin I2; IL, interleukin; NF-kB, nuclear factor kappa B.